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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
JAISLE, CECILIA M	

ART UNIT	PAPER NUMBER
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/578,594	DAL PIAZ ET AL.	
	Examiner	Art Unit	
	CECILIA M. JAISLE	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25 and 28-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-25 and 30* is/are allowed.

6)☒ Claim(s) *28,29 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05-08-2006 and 01-12-2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Rejection Under 35 US 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28, 29 and 31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling treatment of asthma, psoriasis and atopic dermatitis with Formula (I) compounds, does not reasonably enable treatment of all pathological conditions/diseases susceptible to amelioration by phosphodiesterase 4 (PDE4) inhibition (claims 28 and 31), chronic obstructive pulmonary disease (COPD), rheumatoid arthritis (RA) or irritable bowel disease (IBD) (claim 29). The present specification offers no evidence that the claimed compounds control such specific diseases/conditions. The specification otherwise does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with claims 28, 29 and 31.

Many factors require consideration when determining whether sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." MPEP 2164.01(a). These factors include: (1) the claim breadth; (2) the nature of the invention; (3) the state of the prior art; (4) the level of predictability in the art; (5) the amount of direction provided by the inventor; (6) the presence of working examples; and (7) the quantity of experimentation

needed to use the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)(reversing the PTO's determination that claims directed to methods for hepatitis B surface antigen detection did not satisfy the enablement requirement). See also *In re Goodman* 29 USPQ2d 2010, 2013 (Fed.Cir. 1993). Application of these factors to the present application supports the determination that the present disclosure fails to satisfy the enablement requirement:

1. **Breadth of the claims:**

(a) Scope of the compounds. Claims 28, 29 and 31 cover methods using potentially billions of compounds of Formula (I).

(b) Scope of the diseases covered. Claims 28, 29 and 31 recite methods for treating all pathological conditions or diseases susceptible to amelioration by PDE4 inhibition, COPD, RA and IBD, for which the disclosure is non-enabling.

COPD is a collection of progressive airway diseases, characterized by gradual lung function loss. It includes chronic obstructive bronchitis (inflammation and eventual scarring of bronchi) and emphysema (enlargement and destruction of alveoli). Emphysema comes in several forms, including congenital lobar emphysema, bullous emphysema, centrilobular emphysema (proximal acinar emphysema), panacinar (panlobular), distal acinar (paraseptal) as well as Alpha-1 antitrypsin (AAT) deficiency, a genetic form of emphysema. COPD patients often have both bronchitis and emphysema. Ordinary chronic bronchitis is sometimes included with COPD even if there is no actual obstruction, and asthmatic bronchitis is generally included in COPD as well. Persons with COPD typically develop smaller air

passageways, which can become clogged with mucus and have partially destroyed alveoli. There is no pharmaceutical treatment for COPD per se. Treatment is supportive and designed to relieve symptoms and improve quality of life. Oxygen is often given to partially compensate for the loss of lung function. Bronchodilators can expand passageways in the lungs, corticosteroids can reduce inflammation and antibiotics can ward off bacterial infections, but none of these treat COPD itself.

RA is an inflammatory disorder causing destruction of articular cartilage, in which macrophages accumulate in the rheumatoid synovial membrane. Mediators are cytokines, including IL-1, IL-18, α-TNF and IFN. It is thus an autoimmune condition where the body's immune system attacks its joints.

IBD is another illness considered to be associated with PDE4 activity. It is a generic term for an entire disorder family, the most important of which are ulcerative colitis and Crohn's disease. Less common forms include lymphocytic, collagenous, diversion, ischemic and infective colitis, radiation entero-colitis, solitary rectal ulcer syndrome (SRUS), antibiotic associated IBD, Behçet's Syndrome, and Infective Colitis. IBD has a range of known and unknown causes. Ulcerative colitis, Behçet's Syndrome and Crohn's disease, e.g., are idiopathic. Partial tissue death (infarct) due to blood supply blockage, e.g. after major abdom-inal surgery or poor cardiac output in heart disease, can cause ischemic colitis. Radiation therapy for cancer can cause radiation enterocolitis. Infective colitis can arise from bacteria (e.g., shigella, salmonella, campylobacter, E. coli) or viruses (e.g., Norwalk-like virus rotavirus, CMV, HSV). Fecal stream diversion after ileostomy or colostomy can cause

diversion colitis. Treatment depends on form, and some, e.g., radiation enterocolitis and SRUS, have no current effective pharmaceutical treatment.

2. **Nature of the invention and predictability in the art:** The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

Claims 28, 29 and 31 recite therapeutic use of the present compounds in ameliorating COPD, RA and IBD and other diseases/conditions related to PDE-4 inhibitory activity. Various PDE-4 types generally arise from the presence or absence of two unique N-terminal domains called upstream conserved regions 1 and 2 (UCR1 and 2) and other pieces that may be present. UCR1 and UCR2 have been shown to form a module necessary for PDE-4 activation upon cAMP-dependent kinase (PKA) phosphorylation. For example, there are at least five different forms of PDE-4B: PDE-4B1, PDE-4B2 (short form), PDE-4B3, PDE-4B4 and recently discovered, PDE-4B5. Distinct PDE-4A isoforms include PDE-4A1, PDE-4A5, PDE-4A4B, PDE-4A7, PDE-4A8, PDE-4A10 and PDE-4A11. PDE-4D has nine forms, 1-9. These various forms are not necessarily inter-changeable and there is substantial variation in distribution even within the sub-families. PDE-4A1 is abundant in the brain, PDE-4A4B and PDE-4A10 in inflammatory cells, PDE-4A7 in the brain and spleen, and PDE-4A11 is widely distri-buted. The PDE-4D family is generally not seen in inflammatory cells at all. PDE-4D1 is seen in the spleen and heart, PDE-4D2 in the

spleen, PDE-4D3 in brains, lung and kidney, PDE-4D4 and PDE-4D6 in the brain, PDE-4D5 in lung and kidney, PDE-4D7 in the brain and testes, PDE-4D8 in lung, heart and liver, and PDE-4D9 in spleen, heart and lung. Different types are regulated differently. ERK MAP kinases phosphorylate and regulate activity of PDE-4B, PDE-4C and PDE-4D but not PDE-4A isoforms. Reduced PDE-4D activity apparently causes defective RyR2-channel function associated with heart failure and arrhythmias. In dendritic cells (responsible for naive T_h cell priming), PDE-4A is predominantly active, while monocytes mainly express PDE-4B. PDE-4D5 isoform preferentially interacts with signaling scaffold proteins, β-arrestin and RACK1. PDE-4D3 likewise forms a signaling complex with AKAPs such as AKAP450.

Pharmacological activity in general is unpredictable. In applications involving physiological activity, such as the present:

> The first paragraph of 35 U.S.C. §112 effectively requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

Plant Genetic Systems v. DeKalb Genetics, 65 USPQ2d 1452, 1456 (CAFC 2003).

3. **Direction and Guidance:** That provided in the specification is very limited. The dosage range information is meager at best. It is generic, the same for all disorders the specification covers. No specific direction or guidance provides a regimen or dosage effective specifically for conditions other than asthma and atopic dermatitis

4. **State of the prior art:** A report from the European Respiratory Society, Feb. 13, 2007, http://www.newtocopd.com/currentaffairsnews/list751_item17680.aspx,

downloaded Jan. 16, 2008, gives hope regarding the future of **COPD** pharmaceutical therapy: "Although there are currently no effective treatments for COPD, several new classes of anti-inflammatory drugs are now in clinical development and may be useful in treating the inflammation of COPD and chronic comorbid diseases."

Implications for **Rheumatoid Arthritis**

http://www.medscape.com/viewarticle/464104, downloaded Jan. 17, 2008, reports, for potential combined treatment of **RA** with a vascular intestinal peptide and a PDE inhibitor, "...the possibility of a combined approach using VIP [vascular intestinal peptide] together with a PDE inhibitor merits further investigation."

Regarding any relationship between phosphodiesterase inhibitors and IBD, Targan, et al., Inflammatory Bowel Disease: From Bench to Bedside, 2nd Edition, pp. 553-571, 2003 concludes:

> Rolipram [a specific PDE4 inhibitor] is effective in various animal models of chronic T lymphocyte-dependent inflammatory disease, such as adjuvant arthritis and multiple sclerosis, and was shown to reduce mucosal TNF-alpha production in dextran sulfate-induced colitis, thereby preventing tissue damage. The clinical efficacy of rolipram in IBD has not been investigated.

Prehn, et al., J. Clin. Immunol., Vol. 21, No. 5, 2001, pp. 357-364, observed the anomalous results:

> ...thalidomide, which does not inhibit PDE4 at concentrations used clinically, is therapeutic for Crohn's disease [a form of IBD], while a PDE4 inhibitor, pentoxifylline, is without efficacy. ... Results of the pentoxifylline trial support the idea that inhibition of PDE4, and thus of TNF-alpha, may not be useful in treating Crohn's disease.

These articles demonstrate that enablement for such utilities was not established as of the date of filing of this application.

The history of the actual effectiveness of PDE-4 inhibitors is very short. PDE-4 inhibitors have been investigated for disorders ranging from AD to COPD to depression to schizophrenia to chronic lymphocytic leukemia (CLL). Except in the area of asthma, such efforts have met with very little success. As of the time of filing, and indeed up to now, the FDA has not approved any PDE-4 inhibitor for treatment of any disorder. Extensive effort to get cilomilast and roflumilast to be effective against COPD has been without success, evidence of the skill level in this art. Whether these claimed compounds affect the same isoenzymes as cilomilast and roflumilast is not described.

5. **Working Examples:** No examples show treatment of a disorder of claims 28, 29 and 31, except for asthma, psoriasis and atopic dermatitis. The biological data demonstrates PDE4 inhibition, and does not indicate the PDE4 subtype tested. Applicants do not provide highly predictive competent evidence or recognized tests to treat all conditions recited for the claimed compounds.

The compounds are disclosed to inhibit PDE-4 activity and the specification recites that these compounds therefore treat all diseases susceptible to amelioration by PDE-4 inhibition, including COPD, RA or IBD, diseases/conditions for which Applicants provide no competent evidence. Furthermore, Applicants have not provided competent evidence that the instantly disclosed tests are highly predictive for all uses disclosed and embraced by the claim language for the intended host.

Claims 28, 29 and 31 are directed to "treating a subject" and would be understood as covering humans and animals that have the potential to be afflicted with COPD, RA and IBD. No working example shows human therapy.

6. **Skill of those in the art:** The specification indicates that these compounds are potent and selective inhibitors of PDE4 and are thus useful in the treatment of COPD, RA and IBD. The concept that PDE-4 inhibitors could treat such pathological conditions/diseases generally is contrary to what is known about PDE-4 inhibitors. Some PDE4 inhibitors cause vasculitis (blood vessel inflammation), which has hindered PDE-4 inhibitor clinical investigation. Development of SCH-351591 halted because of acute and chronic vasculitis in small to medium sized arteries, and vasculitis was a significant problem with CI-1018 and cilomilast. The PDE-4 inhibitor IC542 triggered a generalized inflammatory response with extensive neutrophil infiltration in the gastrointestinal tract, nearby mesentery and thymus.

The state of the art (e.g., the articles of the European Respiratory Society, Baumer, Implications for Rheumatoid Arthritis, Targan and Prehn, discussed in detail above) supports that successful amelioration of COPD, RA and IBD is a subject for further investigation. See the discussion of PDE-4 above.

7. **Quantity of experimentation needed to make or use the invention.** Based on the disclosure's content, an undue burden would be placed on one skilled in pharmaceutical arts to make and use the invention, since the disclosure gives the skilled artisan inadequate guidance regarding pharmaceutical use, for reasons explained above. The state of the art indicates the requirement for undue experimentation.

The ability of an agent that inhibits PDE-4 to ameliorate all diseases or conditions recited by the present claims remains open to further study and proof.

Substantiation of utility and its scope is required when utility is "speculative," "sufficiently unusual" or not provided. See *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). Also, note *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) regarding types of testing needed to support *in vivo* uses. Applicants' attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 66 FR 1092-1099 (2001), emphasizing that "a claimed invention must have a specific and substantial utility." See also MPEP 2163, *et. seq*. The disclosure in this application is not sufficient to enable the instantly claimed methods based solely on disclosure of inhibition of PDE-4 by compounds of Formula (I).

MPEP 2164.01(a) states,

> A conclusion of lack of enablement means that, based on the evidence regarding each of the above [Wand] factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed.Cir. 1993).

The above consideration justifies that conclusion here; undue experimentation would be required to practice Applicants' invention. Consideration of the above factors demonstrates that this application does not sufficiently enable claims 28, 29 and 31.

Allowable Subject Matter

Claims 1-25 and 30 are allowed. The following is a statement of Examiner's reasons for the indication of allowable subject matter:

WO 2004/058729 (cited by Applicants) describes pyridazin-3-one compounds as PDE4 inhibitors. However, the WO 2004/058729 compounds require an acyl-group in the 5-position, while the present compounds exclude such a substituent. In addition, the claimed compounds are patentable and unobvious over all of the art of record.

Conclusion

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cecilia M. Jaisle, J.D. whose telephone number is 571-272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Cecilia M. Jaisle, J.D.

3/18/2008

/James O. Wilson/

Supervisory Patent Examiner, Art Unit 1624